WS9.9 **The CFTR potentiator ivacaftor corrects defective degranulation of secondary and tertiary granules by cystic fibrosis neutrophils**

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Neutrophils in cystic fibrosis (CF) fail to eradicate pathogens causing lung infections. Studies indicating innate differences in neutrophil activity in CF have illustrated increased release of proteases from primary granules. Little is known about degranulation of secondary granules which is mediated by Rab27a. The novel drug ivacaftor, a CFTR potentiator, restores the function of the G551D mutant CFTR protein and trials have shown promising clinical results. The aim of this study was to evaluate abnormalities in CF circulating neutrophils and to investigate the *in vivo* ability of ivacaftor to correct dysregulated neutrophil activity in patients with CF.
Purified neutrophils were exposed to TNFα ($10\,ng/2\times10^7$cells) for 0, 5, 10 or 20min. Degranulation was investigated by Western blot analysis, ELISA and flow cytometry. Rab27a activation was determined by quantifying bound GTP by coupled enzymatic reaction.
CF neutrophils released 50% and 75% less secondary and tertiary granules, respectively ($p < 0.05$). Upregulation of CD66b, a marker of secondary and tertiary granule release, to the cell surface was decreased by 40% on CF cells ($p < 0.05$). In addition, Rab27a activation was delayed and decreased in CF neutrophils ($p < 0.05$). After one year treatment with ivacaftor, degranulation of cells from patients carrying the G551D mutation increased by 130% to the level of healthy controls ($p < 0.05$). In conclusion, altered Rab27a activation causes decreased degranulation of secondary and tertiary granules in CF neutrophils, an effect corrected by ivacaftor treatment in those with the G551D mutation, thereby potentially improving neutrophil function and bacterial clearance in CF.